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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,550	WILDENBERG ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-31 and 33* is/are pending in the application.

4a) Of the above claim(s) *30,31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 13, 2008 has been entered.

2. The examiner reviewing your application at the PTO has changed. To aid in correlating papers in this application, all further correspondence regarding this application should be directed to examiner Carla Myers.

3. Claims 18-31 and 33 are pending. Claims 18-29 have been examined herein.

Claims 30, 31 and 33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 16, 2007.

4. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn. In particular, the previous rejections of the claims under 35 USC 102 and 103 have been obviated by the amendments to the claims. This action contains new grounds of rejection necessitated by Applicant's amendments to the claims and is made non-final.

Amendments

5. The amendment filed on May 13, 2008 does not comply with the new guidelines for filing claims under 37 CRF 1.121. As set forth in the 37 CFR 1.121, the revised amendment practice requires that "Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered)." See MPEP 714. In the present amendment, claims 30 and 31 are listed with the status identifier of "(withdrawn)." However, the text of these claims has not been presented. Accordingly, all future amendments must comply with the requirements of 37 CFR 1.121 and particularly with the requirement to present the full text of any pending claim, including withdrawn claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112, first paragraph – New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not appear to provide support for the amendment to the claims to recite "mixing non-equal amounts of said sample and said standard."

In the response of May 13, 2008, Applicants point to "Paragraph 0131, lines 1 to 5" as providing support for this amendment.

It is first noted that the paragraphs of the present specification have not been numbered. To the extent that "Paragraph 0131, lines 1 to 5" refers to the paragraph number in PGPUB 20070015159, this paragraph consists of 2 lines and states that:

"[0131] In order to detect aneuploidy in an organism, the method present invention is based on the competitive binding, to a limiting amount of complementary binding agent, of equal amounts of DNA from a sample and a standard of the same organism. "

Thus, para [0131] discloses using equal amounts of sample DNA and standard DNA, but does disclose using non-equal amounts of sample DNA and standard DNA.

To the extent that this statement in the response applies to the first 5 lines of para [0130], this para states:

"[0130] Simultaneous detection of aneuploidy in multiple or all chromosomes of the organism is possible using the multiplex method of detection hereinbefore described. Each binding agent or group of binding agents comprises a polynucleotide that is specific for a particular chromosome (and complementary to the sample and standard polynucleotide sequence from that chromosome), immobilised to a microparticle. The microparticles representing each chromosome are that is distinct from each other on the basis of size, the fluorescent label (if any), fluorescence intensity or a combination of these characteristics. These distinct microparticles may then be assessed individually for binding of the sample and standard. Accordingly, this provides simultaneous measurements for the relative frequency of multiple or all chromosomes in a sample. "

Accordingly, para [0130] also does not provide support for the concept of mixing non-equal amounts of the polynucleotide sample and the polynucleotide standard.

All teachings in the specification indicate that equal quantities of a sample DNA and standard DNA are mixed with the binding agent. See, for example, para [0110] wherein it is stated that:

"[0110] Therefore, if a given amount of DNA from a known control diploid DNA is competed against a like amount of DNA from a given biological sample for a limiting number of binding targets, the DNA's should bind to the targets in their relative frequencies. "

Further, the claims as amended recite mixing non-equal amounts of the sample and the standard. This recitation encompasses mixing volumes of sample and standard

that are different from one another since the term "amount" has not been defined in the specification or claims. However, the specification as originally filed does not provide support for the particular embodiment of a method of mixing different volumes (having the same or different concentrations of DNA) of a sample and a standard.

Accordingly, the specification as originally filed does not appear to provide support for the amendment to the claims to recite "mixing non-equal amounts of said sample and said standard" and particularly does not provide support for the concepts of mixing non-equal quantities of sample DNA and standard DNA or mixing non-equal volumes of polynucleotide samples and polynucleotide standards.

Claim Rejections - 35 USC § 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18-29 are indefinite over the recitation of "detecting aneuploidy in one or more chromosomes of a subject simultaneously" because it is unclear as to what is encompassed by simultaneously detecting aneuploidy in one chromosome. To the extent that the claims encompass detecting aneuploidy in two or more chromosomes simultaneously, the claims omit the essential process steps that would be required to detect aneuploidy in more than one chromosome. That is, the claims recite only steps of detecting aneuploidy per se, but not distinguishing between aneuploidy of one

chromosome from aneuploidy of another chromosome. The claims recite a final step of detecting aneuploidy by comparing the signal of binding of the sample and standard to the binding agent, wherein aneuploidy is determined by unequal binding. While the claims require that the binding agent is attached to a microparticle of a different size and fluorescent label intensity for each chromosome, the claims do not recite any active process steps which determine binding of the sample polynucleotides and standard polynucleotides to the binding agent wherein the binding agents are distinguished from one another based on their size and fluorescent label intensity. Accordingly, the claims omit the essential steps that are required to simultaneously detect a change in the number of two or more particular chromosomes.

Claims 18-29 are indefinite over the recitation of "aneuploidy in one or more chromosomes" because this phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. While it is clear as to what is meant by "chromosomal aneuploidy" (i.e., an abnormal number of chromosomes or the state of having chromosomes in a number that is not the exact multiple of the haploid number), it is unclear as to what is meant by aneuploidy in a chromosome.

Claims 18-29 are indefinite over the recitation of "said aneuploidy being determined by an unequal binding." This phrase is not clearly defined in the specification or claims and there is no art recognized definition for this phrase as it relates to determining aneuploidy. It is unclear, for example, as to whether unequal binding refers to a difference in the quantity of sample polynucleotide hybridized to binding agents as compared to standard polynucleotides hybridized to binding agents,

as determined by a difference in the quantity of signal emitted by hybrids formed by the fluorescently-labeled polynucleotide samples to the binding agents as compared to the fluorescently-labeled polynucleotide standards to the binding agents, or whether unequal binding refers to the specificity of hybridization or the degree to which two sequences that are not fully complementary to one another bind.

Claims 18-29 are indefinite over the recitation of "said sample" and "said standard" because these phrases lack proper antecedent basis (see claim 18, steps (iii)-(iv) and claims 26 and 27). While the claims previously refer to "fluorescently-labeled polynucleotide samples" and "fluorescently- labeled polynucleotide standards," the claims do not previously refer more broadly to "a sample" or "a standard." The recitation of "the sample" and "the standard" (steps (ii) and (iv) in claim 18) also make the claims unclear in that the claims further refer to emission spectra of the sample and standard, whereas it is the fluorescent labels on the fluorescently-labeled polynucleotides which may have a different emission spectra.

Claims 18-29 are indefinite over the recitation of "wherein the fluorescent label on said microparticles, if present" (step (iv) in claim 18). The claims previously require that the microparticles for each chromosome have a distinct fluorescent label intensity. Accordingly, it is unclear as how the fluorescent label can be optional (i.e., "if present"). Also, if the fluorescent label is optional, it is unclear as to how the microparticles can have a different fluorescent label intensity. It is further unclear as to what is intended to be the relationship between the fluorescent label recited in step (iv) of claim 18 and the fluorescent label intensity recited in step (iii) of claim 18. While step (iv) requires that the

fluorescent label is on the microparticles, step (iiii) more broadly recites that the microparticle has a fluorescent label intensity (and thereby, the microparticle may have a fluorescent label incorporated therein, rather than "on" the microparticle). Accordingly, it is unclear as to whether the fluorescent label intensity recited in step (iii) is the intensity for the same fluorescent label recited in step (iv) or for another unspecified fluorescent label.

Claims 27-29 are indefinite over the recitation of "said binding agent comprises a nucleic acid immobilized on a microparticle" (claim 27, lines 1-2) because it is not clear as to how this recitation is intended to further limit the claims from claim 18. Claim 18 requires that the binding agent comprises a polynucleotide immobilized onto microparticles. It is thereby unclear as to whether the binding agent comprises both the polynucleotide and the nucleic acid, or whether the nucleic acid is intended to be the same as the polynucleotide, and/or whether the microparticle attached to the nucleic acid is the same as or distinct from the microparticle attached to the polynucleotide. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 18-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/631,714 in view of Singh et al (WO 02/40698; cited in the IDS of 11/2/06).

The present claims and the claims of '714 are both inclusive of methods for detecting aneuploidy in a subject comprising producing a fluorescently labeled polynucleotide sample and an equivalent non-aneuploid polynucleotide standard, labeled with a different fluorescent (i.e., reporter) molecule, mixing the polynucleotide sample and the polynucleotide standard with a limiting amount of a binding agent, wherein the binding agent comprises a polynucleotide immobilized to a microparticle and detecting aneuploidy by detecting non-equal binding of the polynucleotide sample and standard sample to the binding agent.

The present claims and the claims of '714 differ in that the present claims require that the microparticles to which the binding agent is immobilized are of a distinct size for each binding agent that is to a different chromosome. However, the use of probes/binding agents immobilized onto microparticles of different sizes and having different labels was known in the art at the time the invention was made. In particular,

Singh (page 6, lines 29-33; page 17, lines 5-17) teaches that microparticles of different sizes and different fluorescent emission intensity may be used together in combination to distinguish the binding of a target polynucleotide to one binding agent from the binding of a target polynucleotide to a different binding agent (page 11). It is stated that by using combinations of microparticles of different sizes and labeled with different fluorophores of different emission intensity, multiplex assays can be performed that allow for the simultaneous analysis of multiple targets (page 6, lines 29-33; and page 17). For instance, Singh teaches that a method that uses 10 different microparticles of different sizes, each labeled with one of 10 different fluorophores, will potentially provide 100 different microparticle populations. If each fluorophore is present at a different concentration, then 1,000 different populations of microparticles is possible, allowing for the use of 1,000 different probes in a single multiplex assay (page 17, lines 23-33). In view of the teachings of Singh, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the claims of '714 so as to have used binding agents immobilized to microparticles of different sizes and labeled with different fluorescent labels of different emission intensity in order to have provided the advantage of generating a multiplex assay that could be used to simultaneously analyze for aneuploidy of multiple chromosomal targets.

The present claims and the claims of '714 also differ in that the claims of '714 do not require mixing unequal amounts of the polynucleotide sample and the standard sample. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method claimed in '714 so as to have

used non-equal volumes of the polynucleotide standard and polynucleotide sample when the polynucleotide standard and polynucleotide sample were of different concentrations in order to achieve the objective set forth in the claims of '714 of providing an "equivalent" (and thereby same quantity) of non-aneuploid polynucleotide standard.

Additionally, the present claims and the claims of '714 are also inclusive of methods wherein the subject is a diploid, and particularly a human, cattle, sheep, horse or embryo; methods wherein the embryo is generated by in vitro fertilization; methods wherein the sample originates from a blastomere, somatic cell, a reproductive cell, or a gamete; and methods wherein the microparticle is a silica microparticle and particularly a silica microparticle that is silanized.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21, 23, 24 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel (U.S. Patent No. 6,562,565) in view of Mohammed (PGPUB 2003/0124584), and further in view of Singh et al (WO 02/40698; cited in the IDS of 11/2/06).

Pinkel (col. 2, lines 30-43; col. 3, lines 15-42) teaches a method of determining the copy number of chromosomal sequences (i.e., a method of detecting aneuploidy) comprising the steps of producing fluorescently-labeled test/sample nucleic acids from a subject (col. 3, lines 15-42, col. 10, lines 41-67); producing fluorescently-labeled polynucleotide reference/standard nucleic acids from a normal sample containing two copies of each autosomal sequence and having one or two copies of each sex chromosomal sequence depending on gender (i.e., non-aneuploid fluorescently-labeled polynucleotide standards) wherein the test/sample nucleic acids and the reference/standard nucleic acids are labeled with fluorophores having different emission spectra (col. 3, lines 22-27 and col. 10, lines 41-67); mixing equal quantities of the test/sample nucleic acids and the reference/standard nucleic acids (col. 12, lines 28-38, col. 13, lines 41-50) with a limiting amount of "target nucleic acids" (i.e., nucleic acid binding agents) immobilized onto solid supports that are labeled with a fluorescent moiety; detecting the amount of binding between the test/sample nucleic acids and the

binding agents and the amount of binding between the reference/standard nucleic acids and the binding agents, and comparing the amounts of binding wherein an increase in binding of the test/sample nucleic acids as compared to the reference/standard nucleic acids indicates an increase in copy number and a decrease in the binding of the test/sample nucleic acids as compared to the reference/standard nucleic acids indicates a decrease in copy number (i.e., wherein an unequal binding indicates aneuploidy; column 2, lines 66-67 and column 3, lines 1-6).

In particular, Pinkel teaches that the nucleic acid binding agents may be on separate supports, such as a plurality of beads (column 2, lines 55-56), and that the target elements are typically from 1μM to 3mM (i.e. microparticles, column 4, lines 26-31 and col. 8, lines 59-61). Pinkel also teaches that beads of various sizes can be used (column 8, lines 57-61). Accordingly, Pinkel teaches that the nucleic acid binding agents are immobilized onto microparticles of distinct sizes.

Regarding the recitation in the present claims that the sample and standard nucleic acids are mixed with a limiting amount of binding agents, Pinkel teaches that "Small array members containing small amounts of concentrated target DNA are conveniently used for high complexity comparative hybridizations since the total amount of probe available for binding to each element will be limited. Thus, it is advantageous to have small array members that contain a small amount of concentrated target DNA so that the signal that is obtained is highly localized and bright" (col. 8, line 61 to col. 9, line 1). Accordingly, Pinkel teaches that small amounts of the target nucleic acid/binding agent are present so that limiting amounts of the target/binding agent are available for

binding to the sample and reference nucleic acids. It is noted that the term "limiting" is not defined in the specification or claims and thereby the disclosure of Pinkel of using small amounts of target nucleic acid /binding agent meets the limitation in the claims of a "limiting amount" of binding agent.

Regarding the recitation in the present claims of "mixing non-equal amounts of said sample and said standard," this recitation is considered to include mixing non-equal volumes of the sample and standard since a volume constitutes an amount. Pinkel does not specifically teach using non-equal volumes of the sample and standard.

However, Pinkel does teach that the CGH assay is performed using equal quantities of the test/sample nucleic acid and reference/standard nucleic acid (e.g., col. 13, lines 41-45). Further, Mohammed (para [0004]) teaches that:

"The principle of the array CGH approach is simple. Equitable amounts of total genomic DNA from cells of a test sample and a reference sample (e.g., a sample from cells known to be free of chromosomal aberrations) are differentially labeled with fluorescent dyes and co-hybridized to the array of BACs, which contain the cloned genomic DNA fragments that collectively cover the cell's genome. The resulting co-hybridization produces a fluorescently labeled array, the coloration of which reflects the competitive hybridization of sequences in the test and reference genomic DNAs to the homologous sequences within the arrayed BACs" (emphasis added).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have performed the method of Pinkel using non-equal volumes (i.e., amounts) of the test/sample and standard/reference in those situations in

which the concentration of the polynucleotides in the test/sample and standard/reference were different from one another and the use of different volumes would have ensured that the resulting mixture of polynucleotides contained the same quantity of test/sample and standard/reference polynucleotides, in order to achieve the objectives set forth by Pinkel and Mohammed of providing a competitive hybridization assay that allowed for the determination of the occurrence of a copy number change (aneuploidy) in the test sample.

Further, while Pinkel teaches that the binding agents are immobilized to microparticles that may be of different sizes, Pinkel does not teach that the binding agents for different chromosomes are each immobilized to microparticles of different size and different fluorescent intensity.

However, the use of binding agents immobilized onto microparticles of different sizes and having different labels of different intensities was known in the art at the time the invention was made. In particular, Singh (page 6, lines 29-33; page 17, lines 5-17) teaches that microparticles of different sizes and different fluorescent emission intensity may be used together in combination to distinguish the binding of a target polynucleotide to one binding agent from the binding of another target polynucleotide to a different binding agent (page 11). It is stated that by using combinations of microparticles of different sizes and labeled with different fluorophores of different emission intensity, multiplex assays can be performed that allow for the simultaneous analysis of many different target nucleic acids (page 6, lines 29-33; and page 17). For instance, Singh teaches that a method that uses 10 different microparticles of different

sizes, each labeled with one of 10 different fluorophores, will potentially provide 100 different microparticle populations. If each fluorophore is present at a different concentration, then 1,000 different populations of microparticles is possible, allowing for the use of 1,000 different probes in a single multiplex assay (page 17, lines 23-33).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have immobilized each binding agent specific to a different chromosome to microparticles of different sizes and labeled with different fluorescent labels of different emission intensity in order to have provided the advantage set forth by Singh of generating a multiplex assay that could be used to simultaneously analyze for aneuploidy of multiple chromosomal targets.

Regarding claims 19-21, Pinkel teaches that the test/sample and reference/standard nucleic acids are obtained from a human (i.e., a diploid mammal; see col. 4, lines 16-20; col. 6, lines 31-41; col. 7, lines 36-41; and col. 13, lines 14-16).

Regarding claims 21, 23 and 24, Pinkel does not teach that the subject is an embryo; that said embryo is generated using *in vitro* fertilization; or that said aneuploidy is detected in said embryo prior to implantation of said embryo.

However, Mohammed teaches a method of detecting aneuploidy, wherein said subject is a mammal (page 2, paragraph 0015), said mammal is an embryo generated by *in vitro* fertilization (page 13, paragraph 0119), and said method results in preimplantation genetic diagnosis (i.e. detection of aneuploidy prior to implantation of said embryo) (page 13, paragraph 0119). Mohammed teaches that by analyzing

embryos generated by *in vitro* fertilization prior to implantation of said embryo, abnormal embryos can be distinguished from normal embryos so that only normal embryos are used for implantation (para [0119]).

In view of the teachings of Mohammed, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the CGH method of Pinkel to the analysis of embryos generated by *in vitro* fertilization prior to implantation of said embryo, in order to have provided an effective means for identifying embryos with aneuploidy and thereby of providing a method that permitted the selection of embryos of normal ploidy for transplantation.

Regarding claim 27, Pinkel teaches that the binding agent (target) is a nucleic acid immobilized on a microparticle, and that the nucleic is complementary to and thereby has a binding specificity to the test/sample and reference/standard polynucleotides (column 4, lines 1-7, col. 4 lines 26-31 and col. 8, lines 57-61).

Regarding claim 28, Pinkel does not explicitly state that the microparticles are silica microparticles. However, Pinkel does separately teach immobilizing the binding agent onto microparticles and teaches that methods using arrays of small beads can achieve better sensitivity (col. 8, lines 57-65). Pinkel also teaches covalently attaching nucleic acid binding agents to silica (col. 9, lines 8-11). Pinkel states that fused silica provides a very low fluorescence substrate and a highly efficient hybridization environment (col. 9, lines 8-11) Further, Mohammed (para [0095]) teaches immobilizing nucleic acids onto a solid surface of fused silica. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have

modified the method of Pinkel so as to have immobilized the binding agents onto silica microparticles, because silica provides a very low fluorescence substrate and a highly efficient hybridization environment. Therefore, it would have been prima facie obvious at the time the invention was made to used silica microparticles in the method of Pinkel for detecting aneuploidy, absent evidence to the contrary.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh, and further in view of Ibanez et al (Mol Reprod Dev. 2001 Feb;58(2):166-72).

The teachings of Pinkel, Mohammed and Singh are presented above.

Pinkel does not teach that the test/sample and reference/standard nucleic acids are from a subject that is a livestock animal, and particularly a livestock animal that is a cattle or sheep.

However, Mohammed teaches application of the CGH method to the detection of genetic mosaicism (defined therein as "the presence of two or more chromosomally distinct cell lines" [page 13, paragraph 0118], i.e. detection of aneuploidy between cell lines) in livestock (page 13, paragraph 0120). Mohammed teaches that genetic mosaicism is frequent in transgenic animals produced by pronuclear microinjection. It is stated that a successful method of screening for founder animals for germline mosaicism prior to mating would reduce costs associated with propagation of transgenic lines and improve the efficiency of transgenic livestock production.

Further, Ibanez teaches a method of detecting genetic mosaicism (pages 167-168) and teaches application of this method to the analysis of transgenic cattle and

sheep founder animals (page 166, see introduction; page 171, see conclusion). It is stated that detection of mosaicism in livestock founder animals provides a more economic and faster alternative to breeding (see abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used test/sample and reference/standard nucleic acids obtained from livestock and particularly from cattle and sheep livestock, in order to have achieved the advantages disclosed by Mohammed and Ibanez of permitting the screening of cattle and sheep livestock founder animals for germline mosaicism prior to mating, to thereby reduce the costs associated with the propagation of transgenic lines.

11. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh and further in view of Gvakharia et al (Fertility and Sterility. 2002 Sept; 78(Supplement 1):S229).

The teachings of Pinkel, Mohammed and Singh are presented above. Pinkel does not teach that the test/sample nucleic acids originate from an embryo.

However, as discussed above, Mohammed teaches performing the CGH analysis using an embryo to identify mosaicism in embryos prior to implantation. Mohammed states that the method is used for preimplantation genetic diagnosis. Further, Gvakharia teaches collecting cells from the blastomere stage to perform preimplantation genetic diagnosis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used

test/sample nucleic acids that originated from a blastomere to detect aneuploidy in order to have provided a method that permitted the detection of aneuploidy in blastomeres prior to preimplantation of embryos derived therefrom, thereby facilitating the selection of embryos of normal ploidy for transplantation.

12. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel in view of Mohammed and Singh, and in further view of Bitner et al (US Patent Number 6,787,307).

The teachings of Pinkel, Mohammed and Singh are presented above.

Pinkel does not teach that the silica microparticles are silanized.

However, Mohammed (para [0098]) teaches that the solid surfaces to which the binding agent (probe) are immobilized may comprise a silane that provides a hydroxyl functional group for reaction with an amine group of the nucleic acid in order to facilitate the immobilization of nucleic acids.

Further, Bitner (abstract and col. 11, lines 53-60) teaches a method of detecting nucleic acid sequences in a sample using silica microparticles that are silanized and coupled to nucleic acids.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Pinkel so as to have used silanized silica microparticles in order to have provided an effective means for immobilizing the nucleic acid binding agent to the microparticles.

Response to Remarks:

In the reply of May 13, 2008, Applicants traversed the previous rejections under 35 USC 102 and 103 over Pinkel et al. Applicant's arguments are addressed below to the extent that those arguments apply to the present grounds of rejection.

Applicants state that "The methods of the present invention then deduce the copy number of the chromosome of interest based on a ratio of the signal from the control DNA and the signal from the subject DNA when each are present in equal amounts and the binding agent is limiting. " However, Applicants have in fact amended the claims to recite that "non-equal" amounts of control and sample DNA are present." Accordingly, Applicants arguments are not consistent with the claims as amended.

Applicants assert that "Pinkel never mentions competitive binding and the conclusions in this reference are in no way based on the results of a competitive binding assay."

This argument has been fully considered but is not persuasive. Comparative genomic hybridization (CGH), as taught by Pinkel, is a method well known to rely on competitive hybridization between the sample nucleic acid and the reference/control nucleic acid. Mohammed (para [0004]) clarifies this property of CGH stating that:

"The principle of the array CGH approach is simple. Equitable amounts of total genomic DNA from cells of a test sample and a reference sample (e.g., a sample from cells known to be free of chromosomal aberrations) are differentially labeled with fluorescent dyes and co-hybridized to the array of BACs, which contain the cloned genomic DNA fragments that collectively cover the cell's genome. The resulting co-hybridization produces a fluorescently labeled array, the coloration of which reflects the

competitive hybridization of sequences in the test and reference genomic DNAs to the homologous sequences within the arrayed BACs" (emphasis added).

Further, Pinkel teaches that equal quantities of the sample and reference nucleic acids are mixed and contacted with the binding agent immobilized on the microparticle (see, e.g., col. 13). Pinkel also teaches that "Small array members containing small amounts of concentrated target DNA are conveniently used for high complexity comparative hybridizations since the total amount of probe available for binding to each element will be limited. Thus, it is advantageous to have small array members that contain a small amount of concentrated target DNA so that the signal that is obtained is highly localized and bright" (col. 8, line 61 to col. 9, line 1). Accordingly, Pinkel teaches that the CGH method requires the use of equal quantities of the test/sample and reference/standard nucleic acids and limited amounts of the binding agent and thereby the ordinary artisan would clearly recognize that the CGH method of Pinkel is a competitive binding assay.

Applicants state that "Pinkel's method would fail if it did not have an excess of immobilized binding agent because if the binding sites were saturated, or nearly saturated, under one set of conditions, the method would not be able to detect an increase in copy number as no more target would bind and no more signal would be detected."

This argument has also been fully considered but is not persuasive. Applicants do not to provide any evidence to support their assertion that the method of Pinkel would fail if there was not an excess of immobilized binding agent. Further, this

conclusion is contrary to the teachings of Pinkel which indicate that in fact a limiting amount of immobilized binding agent is used in the CGH method (see col. 8-9, cited above). Moreover, Pinkel clearly teaches that the CGH method is applicable to the detection of either an increase or decrease in copy number (e.g., col. 2, lines 16-22). Pinkel also states that the greater the ratio of the binding to the target, the greater the copy number (col. 11, lines 28-38). Additionally, Mohammed (para [0091] states that "CGH is a molecular cytogenetics approach that can be used to detect regions in a genome undergoing quantitative changes, e.g., gains or losses of sequence or copy numbers." It is also noted that the present claims do not specifically require detecting an increase in copy number, but rather broadly recite detecting aneuploidy which encompasses detecting a decrease in copy number. Accordingly, Applicants arguments are also not persuasive because they are not directed to limitations required by the claims.

Applicants state that their method does not use reference probes and that the claimed method does not attempt to measure binding of reference probes to target elements. These arguments have been fully considered but are not persuasive. It is noted that the terminology used in the Pinkel patent is distinct from that used in the present application. However, the differences in terminology do not distinguish the claimed invention over that of Pinkel. The present claims use the terminology of "equivalent, non-aneuploid fluorescently-labeled polynucleotide standards." Pinkel uses the terminology of "reference probe" to refer to an identical nucleic acid that is obtained from normal/control cells that have two copies of each autosomal sequence and one or

two copies of each sex chromosomal sequence – i.e. "non-aneuploid" (e.g., col. 3, lines21-34). Pinkel refers to the fluorescently-labeled nucleic acids obtained from the control sample that is non-aneuploid as a "probe." Again, the use of term "probe" as opposed to "polynucleotide standards" does not distinguish the claimed invention over that of Pinkel. Accordingly, Applicant's method and the method of Pinkel both include performing a step in which "reference probes" (fluorescently-labeled polynucleotides from a non-aneuploid sample) are contacted with the "target elements" (binding agents immobilized on the microparticles), and the binding of the reference probes to the target elements is quantified in order to determine the relative binding of the reference/standard probes as compared to the test/sample probes.

Applicants response further includes a copy of their "Prior Arguments." These arguments were fully addressed in the Office action of December 13, 2007 and apply equally to the restated arguments set forth in the response of May 13, 2008.

Additionally, it is noted that the response at page 8 asserts that "Pinkel et al teaches away from the use of different amounts of test and sample elements and teaches that equal amounts of test and sample elements are required. "Accordingly, the response acknowledges that Pinkel teaches using equal quantities of the sample and reference nucleic acids. It is noted that the present claims have been amended to recite that the method is one that uses non-equal amounts of the sample and standard. It is also noted that this amendment to the claims is contrary to Applicant's characterization of the claimed invention as set forth on page 7 of the response wherein it is stated that the present invention is based on a method of using equal amounts of DNA from a

sample and a standard. Applicants response is thereby confusing in that the characterization of the claimed invention is distinct from the claims as amended. However, to the extent that the claims encompass methods in which the term "amount" encompasses "volumes", the use of non-equal volumes of the sample and standard/reference nucleic acid in the method of Pinkel would have been obvious to one of ordinary skill in the art at the time the invention was made, as discussed in the above rejection. The ordinary artisan would have been motivated to have used non-equal volumes of the sample and standard/reference polynucleotides in those situations in which the concentration of the polynucleotides in the sample and standard/reference were different from one another and the use of different volumes would have ensured that the resulting mix of polynucleotides contained the same quantity of sample and standard/reference DNA.

The response states that "Pinkel et al teaches away from the use of size, number or fluorescence for multiplexing and teaches the use of only fluorescence intensity for detection. " However, a lack of an example showing the use of microparticles that differ with respect to both size and fluorescent intensity does not constitute a "teaching away." While Pinkel does not exemplify methods in which the microparticles to which different chromosomal probes are bound differ from one another with respect to both their size and fluorescent intensity, Singh has been cited as teaching the advantages of using microparticles having both different sizes and fluorescent intensities in order to permit the analysis of many different target chromosomal sequences simultaneously.

Lastly, the response states that "Pinkel et al does not teach the use of multiple internal controls for fluorescence level testing." This argument has also been fully considered but is not persuasive because it is directed to limitations that are not recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). While the present claims recite producing equivalent, non-aneuploid fluorescently-labeled polynucleotide standards, the claims do not require the use of multiple internal controls for fluorescence level testing.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Carla Myers/

Primary Examiner, Art Unit 1634